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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,646	03/30/2004	Choong-Chin Liew	4231/2055F	3701

29933 7590 10/14/2008
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,646	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52,53,56-63,66-74 and 76-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,53,56-63,66-74 and 76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/08 has been entered.

2. Applicant is reminded of their obligation to provide an interview summary of the interview which occurred 12/5/07. No interview summary has been received.

3. This action is written in response to applicant's correspondence received 7/7/08. Claims 52-53, 56-63, 66-74 and 76-79 are pending and considered herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive to place the claims in condition for allowance for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Claims 67 and 79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

Claim 67 appears to have new matter. The specification does not provide basis for the particular combination of observations required for the claim, namely that CCL expression in a test subject is "is 2.25 times higher" with a "p value of <0.05." The limitation "with a p value of <0.05" does not appear to have basis in the context of differential expression of CLC in a test subject versus healthy subjects.

Claim 79 appears to have new matter. The specification does not provide basis for a claim which broadly states that any time a test subject's RNA expression of CLC is "higher" than the expression of healthy control subjects that expression is classified with that of subjects classified as having schizophrenia. Regarding the expression of CLC, the specification provides only one very specific teaching, while this claim recites a broad genus of "higher" expression values. Table 3Y teaches that the ratio of expression in schizophrenic samples relative to control samples is 2.25, indicating that in the tested samples, CLC was expressed, on average at a 2.25 times higher level in schizophrenic patients versus healthy controls. The specification teaches that the samples included four patients with Schizophrenia and six "control" individuals. Table 3Y teaches that this result is significant p=0.0212. Thus, the broad statement in the claim regarding classifying the subject as a candidate for schizophrenia if the RNA level "is higher" appears to be new matter. Also, the limitation "with a p value of <0.05" does not appear to have basis in the context of differential expression of CLC in a test subject versus healthy subjects.

5. Claims 66-67, 70, 74 and 79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. Claims 52, 53, 55-63, 71, 72, and 73 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting expression of a gene encoding a Charcot-Leyden crystal protein (CLC gene) in a human test subject that has schizophrenia or that is healthy, does not reasonably provide enablement for methods wherein the subject is merely "suspected" of having schizophrenia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. Methods wherein the subject has schizophrenia or is healthy are considered enabled insofar as they could be used in a method of identifying the gene as a candidate biomarker for schizophrenia, for example as claimed in claim 76. Applicant is cautioned that while this scope is enabled, prior art rejections might apply. Further, it is noted that currently, the claims have been interpreted so that subjects that are healthy are excluded from the scope of the claims.

Nature of the invention

Claim 58 is drawn to a method for detecting expression of a gene encoding a Charcot-Leyden crystal protein (CLK1) in a human "test subject." Claims which depend from claim 58 set forth that the detected expression is quantified and compared to quantified level of control RNA encoded by said gene in blood samples of control subjects. Listed control subjects include healthy subjects, subjects having schizophrenia and subjects that do not have schizophrenia. Further dependent claims set forth steps of classifying or identifying the test subject as being a candidate for having schizophrenia depending on the outcome of the comparing steps. The

subject whose gene expression is detected is "suspected" of having schizophrenia. Thus, it is clear that the intended use of claim 58 and those that depend from claim 58 is for classifying or identifying the test subject as being a candidate for having schizophrenia.

Independent claim 70 sets forth a method for screening a human test subject for having schizophrenia and includes similar detection, quantification, and comparing steps, reciting that a test subject is a candidate for having schizophrenia if said level of RNA encoded by said gene in said blood sample of the test subject is 2.25 times higher than that of said healthy control subjects with a p value equal to 0.0212.

The nature of the invention requires the knowledge of a reliable relationship between CLC expression in blood and the presence or indication of schizophrenia.

In claim 79, the invention is drawn to a method a method for classifying CLC gene expression in a human test subject, and sets forth steps of quantifying a level of RNA encoded by a CLC gene, comparing that level to a level of RNA found in blood samples from control subjects having schizophrenia and also comparing it to control subjects who are healthy. The independent claim states that based on particular determinations, the classification of CLC gene expression results either with that of said subjects having schizophrenia or with that of subjects who are healthy.

The nature of the invention requires the knowledge of a reliable association between CLC expression and the ability to classify a particular individual's expression with the expression of subjects having schizophrenia or not having schizophrenia, and further, the use of this method requires that there is an underlying assumption that this classification is meaningful. Reading the claims in light of the specification it is clear that applicant intends to use such a classification

method in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification. Further, the practice of the invention requires an understanding of how the presence of schizophrenia effects the level of CLC expression in human blood in patients having schizophrenia versus patients that do not have schizophrenia but may have some other disorders.

Scope of the claims

In claim 61, the health status of the control individuals is entirely undefined, and encompass subjects with schizophrenia, healthy patients, patients with some other disease, such as depression, manic depression syndrome, rheumatoid arthritis or multiple sclerosis.

Claim 68 is representative of the narrowest claims set forth in the instant claim set that sets forth relationships that are supported by the data in the specification. This claim specifically defines the control population as healthy subjects and sets forth a very particular ratio of gene expression in the test subject relative the healthy control subjects.

Teachings in the Specification/Examples

Regarding schizophrenia, the specification provides example 27 wherein gene expression profiles of blood samples from individuals having schizophrenia were compared with normal individuals, that is healthy patients. The specification teaches that 1,952 genes were identified as being differentially expressed, and regarding the instant claims, table 3Y provides a list of these genes (Example 27). CLC is among the genes.

Table 3Y teaches that the ratio of expression in schizophrenic samples relative to control samples is 2.25, indicating that in the tested samples, CLC was expressed, on average at a 2.25 times higher level in schizophrenic patients versus healthy controls. The specification teaches

that the samples included four patients with schizophrenia and six "control" individuals. Table 3Y teaches that this result is significant p=0.0212.

The specification further provides example 51 which compares gene expression in patients having schizophrenia versus patients having manic depression syndrome. The specification teaches that 294 genes were identified as being differentially expressed, and regarding the instant claims, table 3AC provides a list of these genes (Example 51). CLC is not among the genes, suggesting that this gene is not differentially expressed in Schizophrenic patients versus patients with manic depression syndrome.

Claim 79 is inclusive of methods which classify CLC expression of a subject as "with that of schizophrenia" based on any observation of any "higher" CLC expression ($p<0.05$) relative to healthy controls, yet the specification teaches that 2.25 fold difference in expression was observed.

Claim 62 is inclusive of control subjects of any health status. For example, the claims are inclusive of control subjects that have manic depression syndrome. For this embodiment of the claims, the specification does not provide information about an essential aspect of the invention, namely, evidence that there is a difference in expression of the CLC gene between these two populations.

Furthermore, though the specification teaches that this gene is differentially expressed in schizophrenia patients versus healthy patients, the specification teaches this is true for thousands of genes. There is no guidance or analysis of data in the specification to suggest that this gene in particular is sufficient to classify a patient as a candidate for schizophrenia, as instant claimed.

This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

State of the Prior Art and Level of Unpredictability

Observing differences in expression between two populations is a highly unpredictable endeavor. While the instant specification teaches that CLC is differentially expressed in a population of schizophrenia patients versus control subjects, the specification does not establish that any particular level of expression of CLC (relative level or raw level) is sufficient to reliably classify expression of a test subject with that of subjects having schizophrenia or to reliably identify a patient as a candidate for having schizophrenia.

The expression of genes in example 27 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication of experiments in the instant specification.

To this end, Sharp et al. (US 2007/0059745) teach methods for identifying differentially expressed genes in blood samples of patients with schizophrenia versus those without schizophrenia (Example 12, page 36, with exemplary results given in Figure 9 and Table 12a and

12b). Sharp et al. teach that the methods used are given in Example 4, which is given on page 24. Example 4 teaches a method comprising detecting RNA encoded by genes in blood samples of human patients afflicted with schizophrenia using an oligonucleotide of predetermined sequence. Namely, the example teaches using microarray analysis with RNA being applied to Affymetrix chips, namely the U95A chip. This chip inherently has thereupon probes for the detection of CLC gene. Sharp et al. report the genes they identified as differentially expressed in their analysis but these lists do not include CLC. Thus, it appears that Sharp et al. did not identify this gene as being differentially expressed in what appears to be a very similar study. Sharp et al. used a different sample type than applicants used in their analysis, however the claims are inclusive of the sampling methods used by Sharp et al. Further, it is difficult to predict or know the fact that Sharp et al. did not observe the same result as applicant is due to different RNA source or if it is because the results observed in the instant specification cannot be reliable reproduced.

Fjaerli et al. teach that CLC is downregulated in whole blood of infants hospitalized with respiratory syncytial virus This exemplifies that it is highly unpredictable whether or not one can conclude, simply from a blood sample of a test patient, that schizophrenia is present, since differential expression versus a control could indicate some other disorder or phenotype is present, whether that is respiratory syncytial virus, manic depressive disorder or some other disease which has not yet been analyzed.

Iwamoto et al. teach that expression profiling in psychiatric fields have been notoriously discordant, with different studies often reporting conflicting gene expression data (The Neuroscientist, Vol. 12, Number 4, 2006, pages 349-361; Abstract and page 351). Tsuang et al.

undertake an analysis that is very similar to the one in the instant specification, with one major difference being that their sample size is larger. Regarding their results, Tsuang et al. caution that the results must be interpreted with caution given several limitations including small sample size, the fact that the findings are not replicated in a separate cohort and results "may represent chance findings and type-I inferential errors," and that the patients tested were all on drugs that were not accounted for in the analysis (American Journal of Medical Genetics, Part B (Neuropsychiatric Genetics) 133B:1-5(2005)). All of these cautions set forth by Tsuang et al. appear to be equally or more relevant to the study set forth in the instant application, where very small sample sizes were used with no apparent correction for effects of medication on the observations. Vawter et al. teach that there is lack of consistency in the study of genes differentially expressed in schizophrenia which might be related to etiological and genetic heterogeneity of the illness (p. 42, Vawter et al. Schizophrenia Research, Vol. 67, pages 41-52, 2004). All of these taken together underscore and highlight the very unpredictable nature of this technology area.

Furthermore, although CLC was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and unpredictable whether it would be expressed in the blood of patients having other mental illnesses or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls. It is unpredictable whether the gene is differentially expressed, for example, in patients having manic depression disorder versus healthy controls, and if it is, how this relates to the difference in expression between patients with schizophrenia

and manic depression disorder. A method for classifying subjects which relies on a comparison between expression in the blood of a test subject and control subjects requires the knowledge of this information in order to reliably make suggestions or drawn conclusions about the presence of schizophrenia, as set forth in the claims.

The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is sufficient to conclude that a patient is a candidate for schizophrenia or that their expression level should be "classified" with patients having schizophrenia. Furthermore, the specification has not shown that all expression at a level statistically the same as that observed in a population of patients having schizophrenia is sufficient to conclude that schizophrenia is present. In fact, it is unclear if this is a fair conclusion given the fact that CLC is not differentially expressed in patients having schizophrenia versus manic depression syndrome- the same expression might indicate the presence of manic depression syndrome. It is entirely unpredictable if this is also the case with other diseases. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. All of these inquiries are particularly important in this case since the claims suggest or explicitly recite the intended use of classifying individuals and their expression levels.

Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control expression of CLC in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control group is sufficient to conclude that the test subject is a candidate for the recited schizophrenia. Because some of the claims encompass any level of altered gene expression, it is relevant to

point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a schizophrenia or the absence of schizophrenia.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of CLC gene expression must be observed to successfully conclude that schizophrenia is present. Although the specification teaches there are differences in CLC levels in a schizophrenia population versus a control patient population, and the specification teaches that for this population the difference is a 2.25 fold increase, the specification does not support the assertion in the some of claims that observing such an increase relative to any and all control populations of 2 or more individual is sufficient to suggest schizophrenia is present. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would have to begin by validating the results observed in the instant specification in a separate population of healthy and schizophrenic patients, in view of the established level of unpredictability in this technology area. One would have to further complete similar analysis for other diseases and conditions and control populations versus healthy controls and versus schizophrenic controls in order to attempt to establish when and if analysis of CLC expression is sufficient to suggest schizophrenia is present. For example, consider the comparison of a test result and a control population of individuals with manic depression. If the test result is different from the level of expression observed in the manic depression control group, does this mean schizophrenia is present? Or if

the control population is healthy individuals, how different from the average level of expression of healthy individuals would the test result have to be to indicate schizophrenia- is a 2.25 fold difference required or a higher or lower threshold? Some of the claims recite that any higher difference is sufficient or at least two times fold. The specification does not provide sufficient data for one of skill in the art to know what level is sufficient. Would any difference, up or down regulation be indicative of schizophrenia? Or could one result indicate schizophrenia and one a different disease such as RSV? Is CLC expressed in the blood of individuals with a disease other than schizophrenia or RSV? Is this expression also suggestive of other mental illnesses or other disorders entirely unrelated to schizophrenia? In order to reliably use a method for detecting schizophrenia, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's study. Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of CLC in a test subject and comparing this expression to control subjects, wherein the results are used to "classify the expression" or to suggest that an individual is a candidate for having schizophrenia. The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification

provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Although some of claims are drawn to a method of "detecting expression" or "classifying expression," and not to diagnosis or identifying increased likelihood of disease or the like, it is critical to understand how the classification can be used in order use the claimed invention. In this case, the specification does not provide sufficient guidance as to how to use the detecting or classification methods, or in other words what is the meaning of classifying expression "with that of subjects having" liver cancer or with subjects who are healthy? While one could do the method steps as written, thus satisfying the "how to make" aspect of 112 1st paragraph, the specification does not provide sufficient disclosure to satisfy the how to use aspect of the requirement.

Claims 68 and 70 represent a very narrow embodiment of the claimed invention, but still are based on data that is not replicated. As discussed in the rejection, it is established that the technology on which the instant claims is based is a highly unpredictable technology, and in the face of such a high level of unpredictability, replication is necessary before results can be considered sufficient to support claims directed at classifying the gene expression of an individual test subject. Therefore, even this claim, after having considered all of the factors set forth in this rejection, lacks proper enablement.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 52, 53, 57, 58, 60, 61, 62, 63, 71, 72, 73, 76, 77, and 78 are rejected under 35 U.S.C. 102(e) as being anticipated by Sharp et al.

Sharp et al. teach methods for identifying differentially expressed genes in blood samples of patients with schizophrenia versus those without schizophrenia (Example 12, page 36, with exemplary results given in Figure 9 and Table 12a and 12b). Sharp et al. teach that the methods used are given in Example 4, which is given on page 24. Example 4 teaches a method comprising detecting RNA encoded by genes in blood samples of human patients afflicted with schizophrenia using an oligonucleotide of predetermined sequence. Namely, the example teaches using microarray analysis with RNA being applied to Affymetrix chips, namely the U95A chip. This chip inherently has thereupon probes for the detection of CLC gene. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression. Sharp et al. further teach that the chips were scanned and processed according to manufacturer's instructions, a process which inherently includes detecting and quantifying a level of RNA encoded by every gene on the array, including the CLC gene. Sharp et al. teach that genes that are expressed over two-fold compared to normals are considered as differentially expressed, thus, Sharp et al. teach the step of comparing the level quantified from the patients having schizophrenia with a quantified level of control RNA encoded by said CLC gene in blood samples of healthy control subjects. Due to the fact that the rejected claims are drawn using

comprising language, and the methods of Sharp et al. were inherently carried out for every gene on the Affymetrix U95A chip, the teachings of Sharp et al. anticipate the rejected invention.

Sharp et al. would inherently have detected CLC expression, at some level, in the patients identified as having schizophrenia. For the purpose of claim 58, and its dependents, these are considered patients "suspected" as having schizophrenia.

Sharp et al. report the genes identified as differentially expressed in their table 12a and 12b. A CLC gene is not included in this table, neither do the rejected claims 76, 77, and 78 positively require identifying the CLC gene as a marker, they merely set forth a means by which such an identification might be made. The final clause of claim 76 does not make any structural requirement on the practice of the method, and it does not appear to functionally distinguish the claimed method from that which was inherent to the practice of Sharp et al.

This rejection is applied to claim 71, 72, 73 and 77 because Sharp et al. begin with whole blood samples, thus the blood samples of said human blood samples are whole blood samples. The comprising nature of the claims allows for additional isolation. Further it is noted that Sharp et al. do teach that tested blood can include all nucleated cells (¶0042).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 52, 53, 57, 58, 60, 61, 62, 63, 71, 72, 73, 76, 77, and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuromitsu et al. (Gene Expression Patterns 1(2001) 17-21) in view of Sharma et al. (WO 98/49342).

Kuromitsu et al. teach a method for detecting expression of CLC gene in a human test subject suspected of having schizophrenia comprising detecting RNA encoded by said gene in said subject using an oligonucleotide of predetermined sequence which is specific for RNA encoded by said gene and/or for cDNA complementary to RNA encoded by said gene.

In particular Kuromitsu et al. teach using DNA chip expression analysis using the Hu6800 chip provided by Affymetrix. This chip inherently has thereupon probes for the analysis of CLC expression, and by using this chip they inherently tested for and detected any expression of this gene. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression. In this rejection the "subject suspected of having schizophrenia" is any one of the test subjects who has schizophrenia. Expression that was at least two fold different was classified as differently expressed thus, the test subjects' expression was classified as that of a person having schizophrenia versus healthy controls when there was a two fold difference (p. 18) and if the p value was <0.05 (p. 19). These ranges include the values set forth in claim 76, an thus if they were detected by Kuromitsu et al. they would be considered to indicate differentially expressed genes based on the express teachings of Kuromitsu et al.

Kuromitsu et al. do not teach detecting applying their analysis to the gene expression in a blood sample, and in particular detecting CLC in a blood sample.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a

method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Sharma et al. teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5). Sharma et al. specifically suggest that this method can be applied to the study of schizophrenia (p 6, 3rd ¶).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Kuromitsu et al. so as to have additionally tested the blood of the patients having schizophrenia and the healthy control samples. One would have been so motivated by the express teachings of Sharma et al. that disease exerts a global effect on individuals and that this effect can be measured by gene expression in the blood. The identification of markers for disease in the blood suggests a potential minimally invasive method to detect this disorder of the brain- an organ whose

sampling is very dangerous for patients. One would have been motivated to continue to use the microarray analysis taught by Kuromitsu et al. since they teach that this new technology "enables large-scale coordinated monitoring of gene expression" in an "unprecedented" fashion (p. 17).

Response to Remarks

The rejections for new matter have been modified to address the amended claims. Applicant traverses the rejections beginning on page 8 of the response. The traversal is germane only to the rejections which have been dropped, and thus, is not persuasive to overcome the instantly pending rejections.

The rejection under 112 1st paragraph for lack of enablement has been amended to address the amended and claims. Applicant traverses the rejection insofar is it applies to the pending claims, beginning on page 10 of the response.

Applicant states that the rejected methods can be used in methods of classifying expression of a CLC gene in a human subject (not classifying a subject). First, applicant's statement does not make sense relative to claims 66, 67, and 68 which positively recite "identifying said test subject as being a candidate for having schizophrenia." Second, the issue at hand includes a consideration of the enabled use for methods of classifying expression of CLC in a human subject. That is for claims 58, 59, 60, 61, 62, 63, 71, 72, and 73 which could be used "for classifying expression of a CLC gene in a human subject" there does not appear to be an enabled use, for all of the reasons discussed in the rejection. Applicant further states that these methods can be used in the methods of identifying a gene in coding a CLC protein as a candidate biomarker for schizophrenia in a human test subject. However, it does not appear that this intended use could be reasonable applied to the methods of claims 58, 59 and dependent claims

because the subjects in these claims are identified as those "suspected" as having schizophrenia. In order to be reasonable used in methods for identifying the gene as a biomarker for schizophrenia, it would appear that the subjects would have to be identified as having schizophrenia, not suspected as having so.

Applicant refers to a comment in the previous office action regarding claim 58. However, the reference to claim 58 was a typographical error which is corrected in this office action. Any inconvenience is regretted. Claim 58 as previously set forth, and as currently set forth did not and does not represent a very narrow embodiment of the claimed invention, to the contrary it is one of the broadest claims. Nonetheless, applicant's comments are addressed. Applicant states that multiple subjects tested per positive and negative control groups in the reduction to practice inherently constitutes replication. It is noted that only pooled results are given, and to that end, the only results given are an average fold change in healthy versus ill subjects. While this does demonstrate that the actual detection of expression can be carried out in healthy and control subjects, as noted in the rejection, this is not the issue. The issue here is how to use the claimed invention. The fact that multiple individuals were tested does not constitute a replication of the entire experiment, were average values from each group were compared. The rejection cites references to support the idea that this is a highly unpredictable area of endeavor and that replication is necessary. For example, Lee teaches that replication is necessary to begin to screen out false positive results since the platform used for discovery is so prone to identification of false positive results. Further, following the caution of Tsuang et al. it is noted that it does not appear that any correction was made for the possibility that the patients

with schizophrenia were on medications, nor the potential effects that these medications would have had on the CLC expression in the blood.

Applicant disagrees with the examiner's position that the specification does not provide sufficient guidance as to how to use the detecting or classification methods. Applicant states that the specification describes that the methods can be used in class prediction analysis. However, before the methods can reliably and reasonably be used in class prediction analysis, it is necessary to provide adequate evidence that the relationship observed in the specification is reliable and reproducible, as suggested by the references cited in the rejection, especially Lee and Tsuang et al. Further, even applicant's specification supports this position as it states in ¶ 0124 that methods for class prediction analysis include a training phase and a testing phase. Here the testing phase is yet to be carried out.

Applicant reiterates the position that claim 79, drawn to a method of classifying expression of a gene encoding a CLC protein in a human subject is fully enabled. However, this claim is only as meaningful as the relationship set forth in the specification. Since, this result is not replicated, at the time the invention was made, one skilled in the art would not have a measure of the reliability of the relationship, given the state of the art at the time the invention was made.

Applicant points out on page 14 of the remarks that the comparison step of claim 79 is between a test subject and two control groups- healthy controls and those with schizophrenia, and provides further discussion about why the issue regarding whether or not CLC is differentially expressed in other diseases does not preclude the enablement of the claimed invention. This discussion in the rejection remains included to address claims which require

comparison to a control but do not define the control. Thus, this issue is relevant if the control individuals, for example have manic depression or other diseases.

Applicant traverses the rejection under 103 beginning on page 15 of the response. Applicant states that the generic teaching by Sharma is not sufficient motivation to apply the teachings of Kuromitsu et al. to detect expression of CLC in blood of a human test subject because it provides no substantive scientific basis to predictably arrive at the claimed invention of identifying CLC gene as a candidate marker for schizophrenia based on its specification. First, KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. The instant claim is drawn using "comprising" language, and as such encompasses methods where hundreds or thousands of genes may be tested for to be potential biomarkers all at once. This is the type of embodiment addressed in this rejection. Here the first reference teaches using a microarray to screen brain tissue for potential biomarkers of schizophrenia, and the second clearly teaches that blood is an appropriate place to look for biomarkers for diseases, including schizophrenia, which is specifically mentioned. The method of the combined references inherently would have included a step of detecting CLC in the blood of those identified as having schizophrenia- as this would have inherently occurred when the RNA samples isolated from the blood were applied to the microarray taught by Kuromitsu et al., albeit along with the expression of many other genes. The active process steps of claim 76 include steps of detecting, quantifying, and comparing which would all have been met for every single gene that is on the array used by Kuromitsu et al. in the method of the combined references. Thus, in this case, applicant's suggestion that motivation specifically related to CLC

is required has not only been foreclosed by KSR, but is also unnecessary given the nature of the rejection.

Applicant argues that Sharma's teachings do not necessarily apply to every disease. Whether or not this is true is irrelevant since Sharma specifically teach that they apply to schizophrenia. Applicant has not provided any credible evidence to contradict Sharma's assertion, and as such, applicant's statements are treated as attorney arguments which cannot take the place of evidence on the record.

Here, applicant is claiming a method for determining if a particular gene is or is not a marker. Applicant argues that the rejection does not meet the criteria for obvious substitution of one known element for another because the result was unpredictable. However, this is not persuasive because it was entirely predictable that the steps could successfully be carried out for every single gene on the array- that is, the samples could be isolated, applied to the array, the results could be detected and compared. While it was not predictable precisely which of the genes would have been identified as differentially expressed, this would be an inherent property of the practice of the assay as applicant has stated it in the claims. That is, in every claim, the practice of the active process steps are entirely predictable. And, Kuromitsu et al. in view of Sharma provide for the practice of the claimed methods for the same purpose- that is to determine genes that are differentially expressed in patients having schizophrenia versus those that do not have schizophrenia. Since the references teach that expression that was at least two fold different was classified as differently expressed thus, the test subjects' expression was classified as that of a person having schizophrenia versus healthy controls when there was a two fold difference (p. 18) and if the p value was <0.05 (p. 19). These ranges include the values set

forth in claim 76, an thus if they were detected by Kuromitsu et al. they would be considered to indicate differentially expressed genes based on the express teachings of Kuromitsu et al. Thus every element of claim 76 would have been a necessary property of the practice of the method taught by the references.

The rejection is maintained.

A new prior art rejection is also set forth in view of a newly identified reference.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

13. Shalit et al. (J Allergy Clin Immunol, Vol. 98, No. 2, August 1996) teach the detection of CLC in blood cells using gene specific primers. They fail to teach the expression of the blood of individuals suspected of having schizophrenia. Thus, since independent claim 58 requires that the test subject is "suspected of having schizophrenia" the population of potential subjects is limited by this recitation and Shalit et al. do not anticipate the instantly claimed invention. It is noted, however, that the instant disclosure is not the first evidence that the mRNA of this particular gene was present in human blood.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday, or Wednesday, from 9:00 AM until 4:30 PM, and Friday from 12:30 until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

October 14, 2008